Where the Pipe Ends: Antibiotics and Antibiotic Resistance in the Ambient Environment

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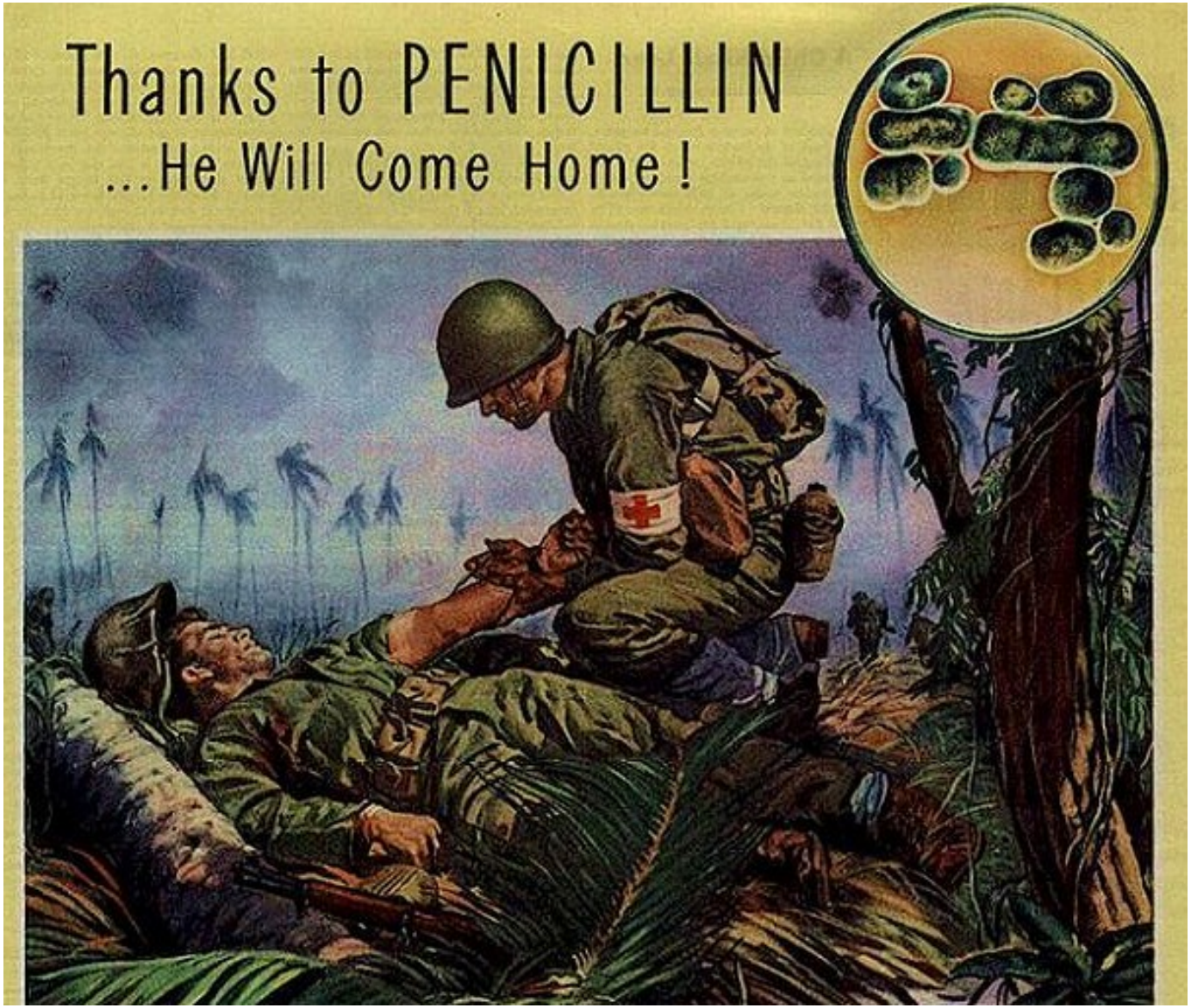
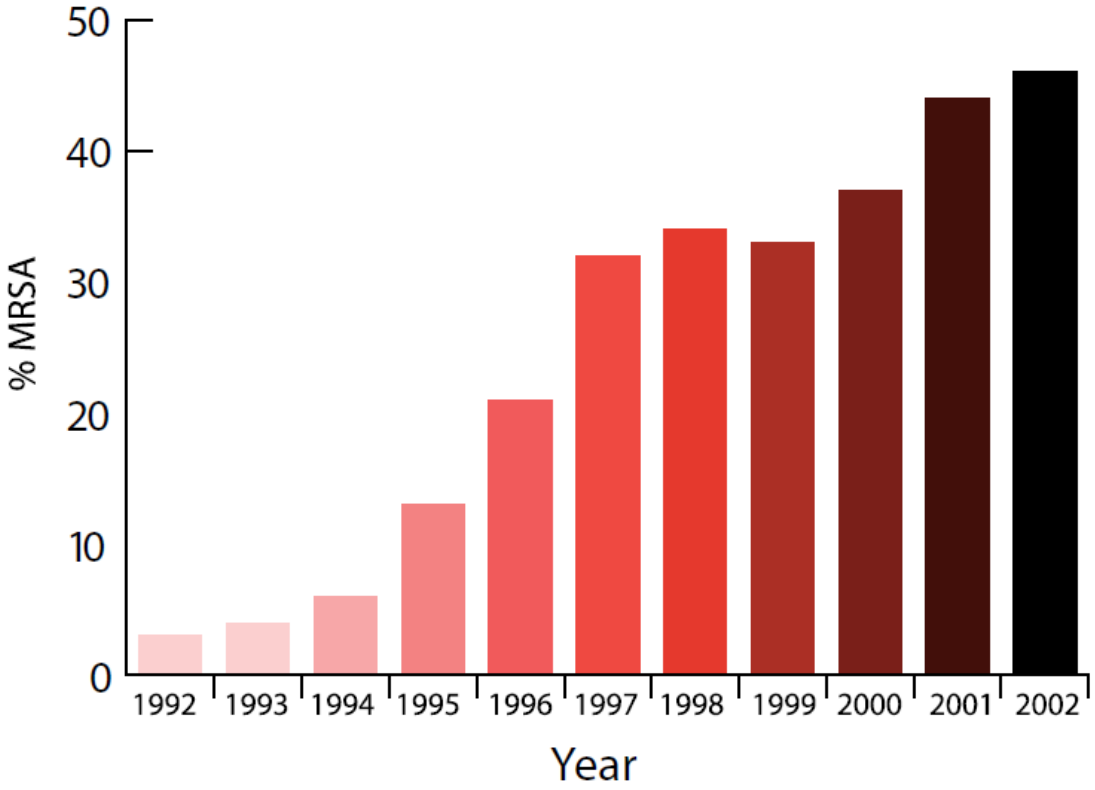
Antibiotics: Significance



http://textbookofbacteriology.net

Antibiotic resistance

The frequency of Methicillin-resistant *Staphylococcus aureus* (MRSA) among blood cultures in England and Wales 1992-2002



- Major public health concern
- A lot of research focused on hospitals
- Emerging concern about resistance in environment

Nordberg, et al. http://soapimg.icecube.snowfall.se/stopresistance/Priority_Medicine_Antibacterial_background_docs_final.pdf

Antibiotic resistance in the ambient aquatic environment

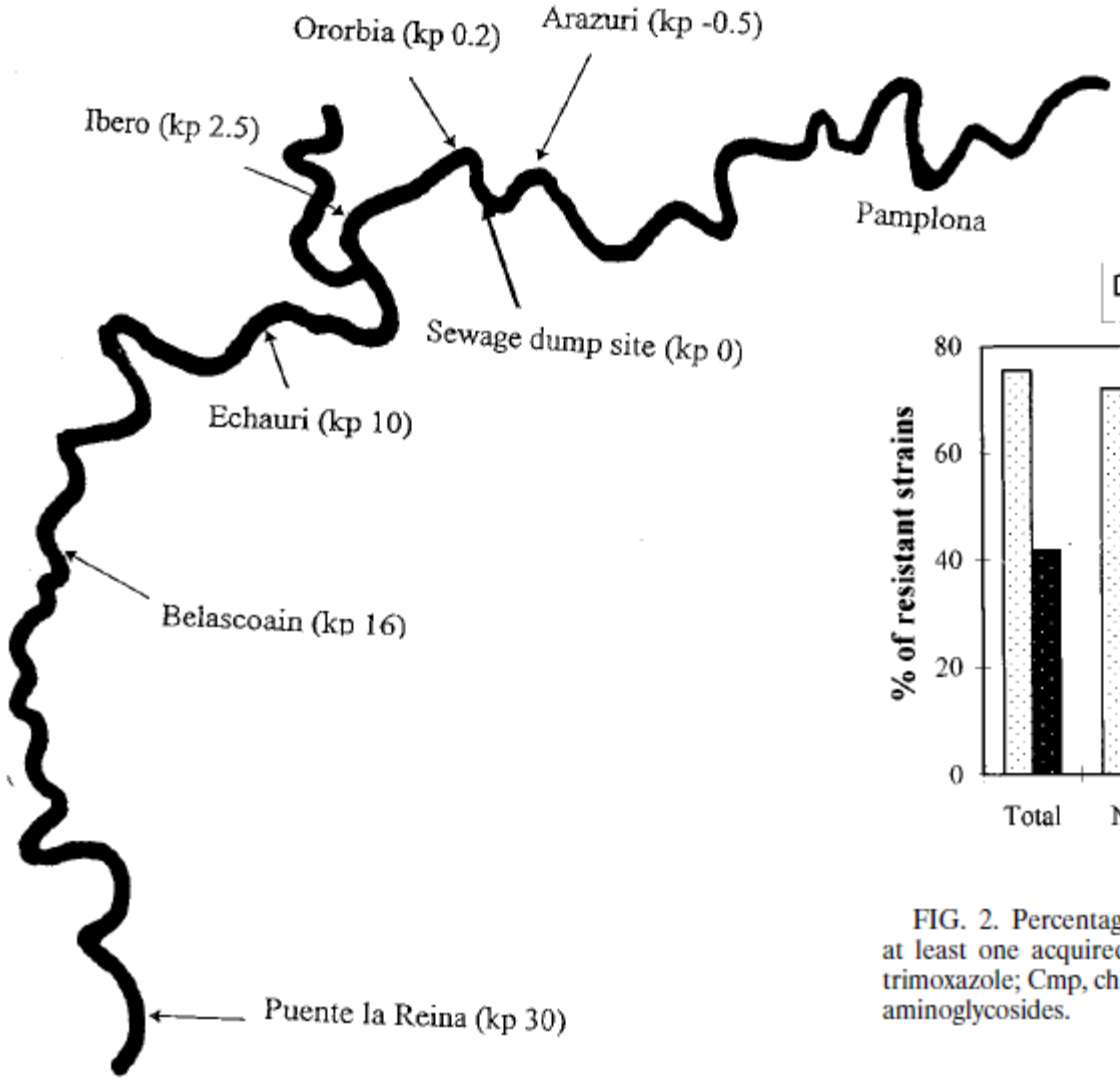


FIG. 1. Locations of sampling sites in the Arga River. kp, kilometric point.

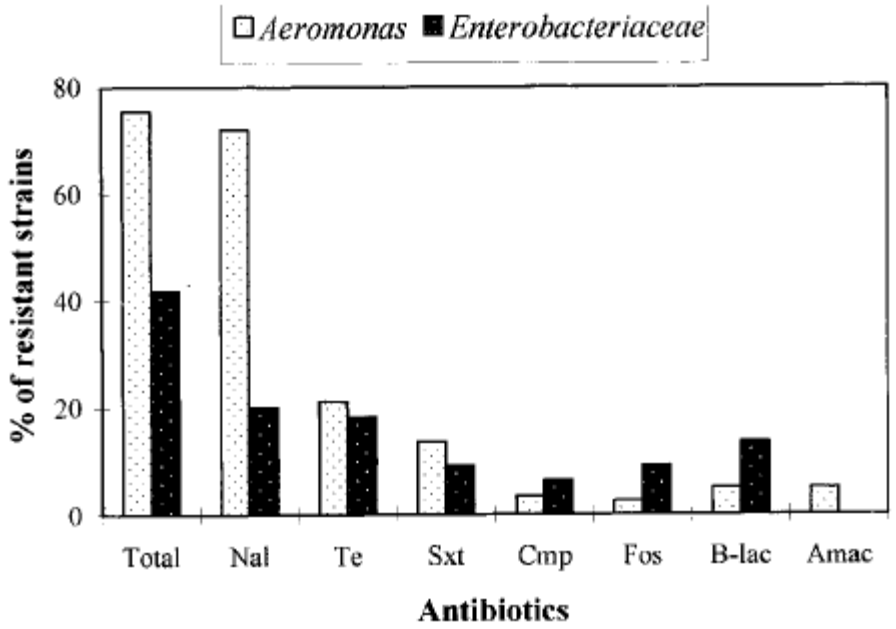


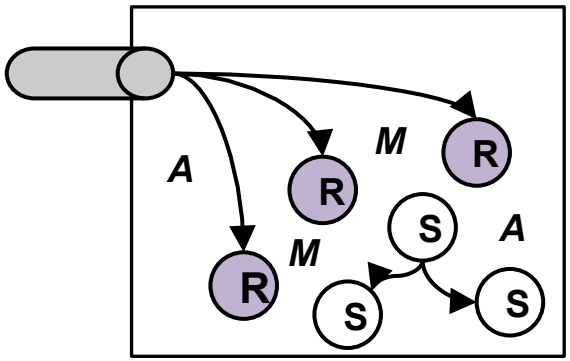
FIG. 2. Percentages of strains resistant to antibiotics. Total, strains showing at least one acquired resistance; Nal, nalidixic acid; Te, tetracycline; Sxt, co-trimoxazole; Cmp, chloramphenicol; Fos, fosfomycin, B-lac, beta-lactams; Amac, aminoglycosides.

Goñi-Urriza et al., *AEM*, 2000.

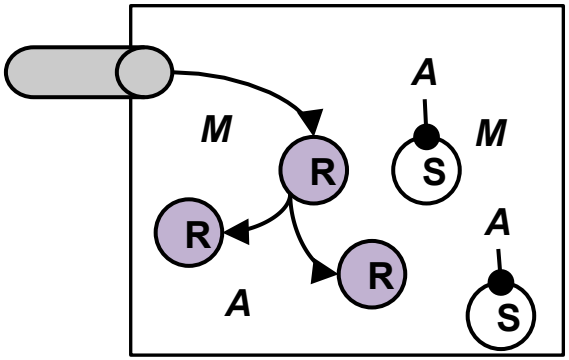
Why are they there?

3 scenarios (hypotheses):

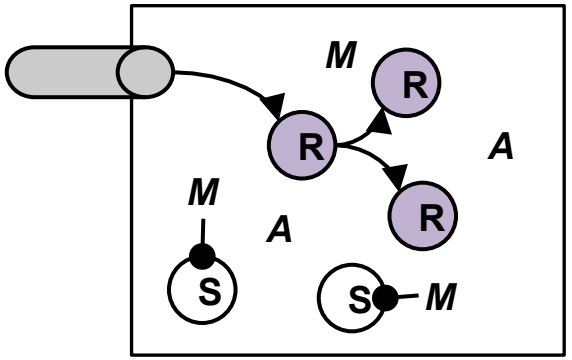
<u>Scenario H1:</u>
Large input
No growth



<u>Scenario H2:</u>
Small input
Antibiotic selection



<u>Scenario H3:</u>
Small input
Metals selection

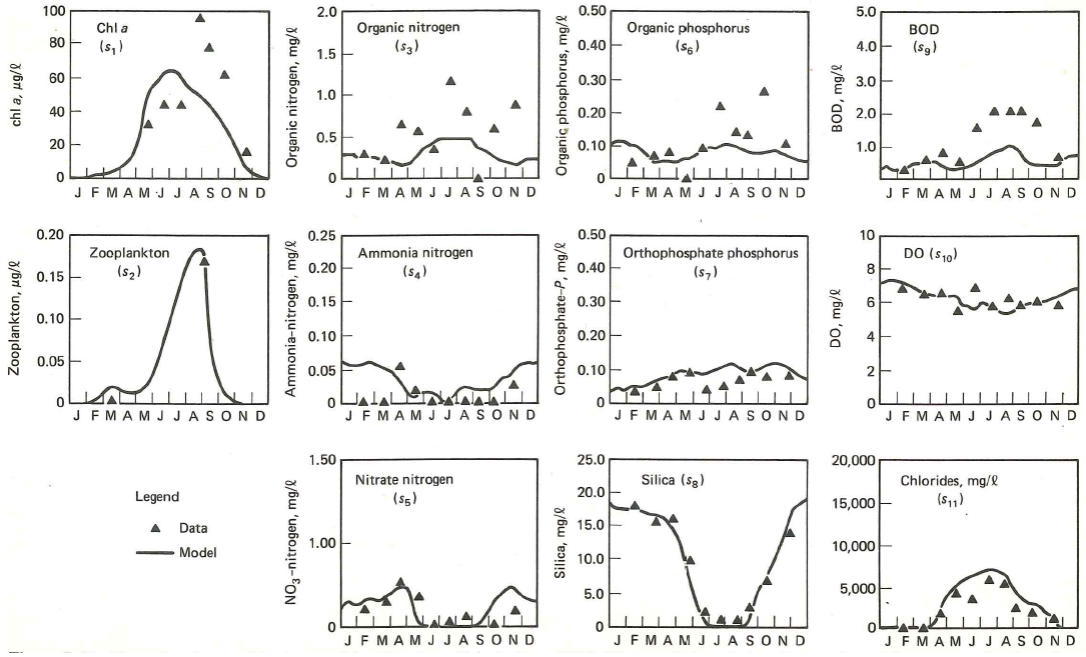


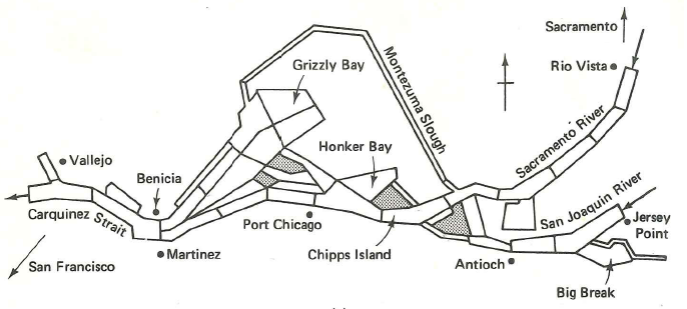
A Antibiotic ***M*** Metal (S) Susceptible bacteria (R) Resistant bacteria

Water Quality Modeling

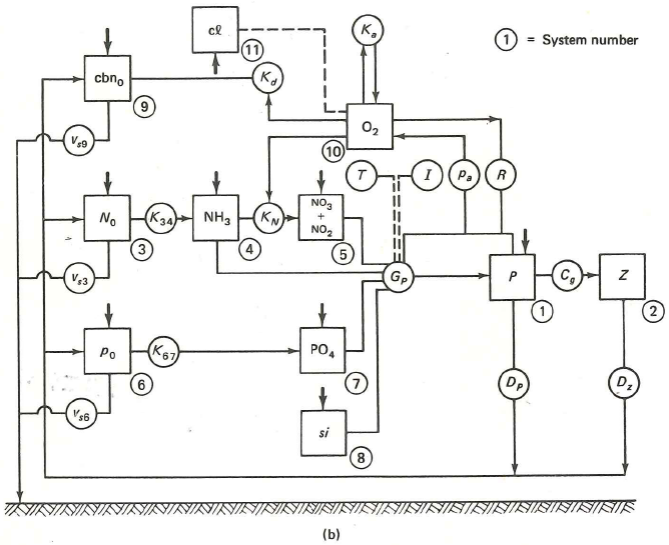
Models are important tools for <u>managing</u> and <u>understanding</u> environmental systems

- Relating discharges to ambient conditions
- Interpreting field observations
- Hypothesis testing





(a)

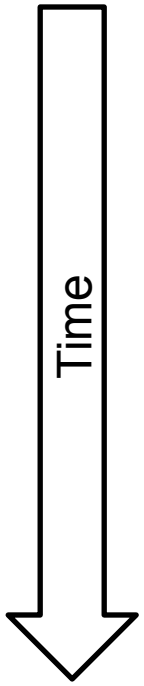


(b)

Eutrophication Model of Sacramento-San Joaquin Estuary, Thomann & Mueller (1987), HydroQual (1981).

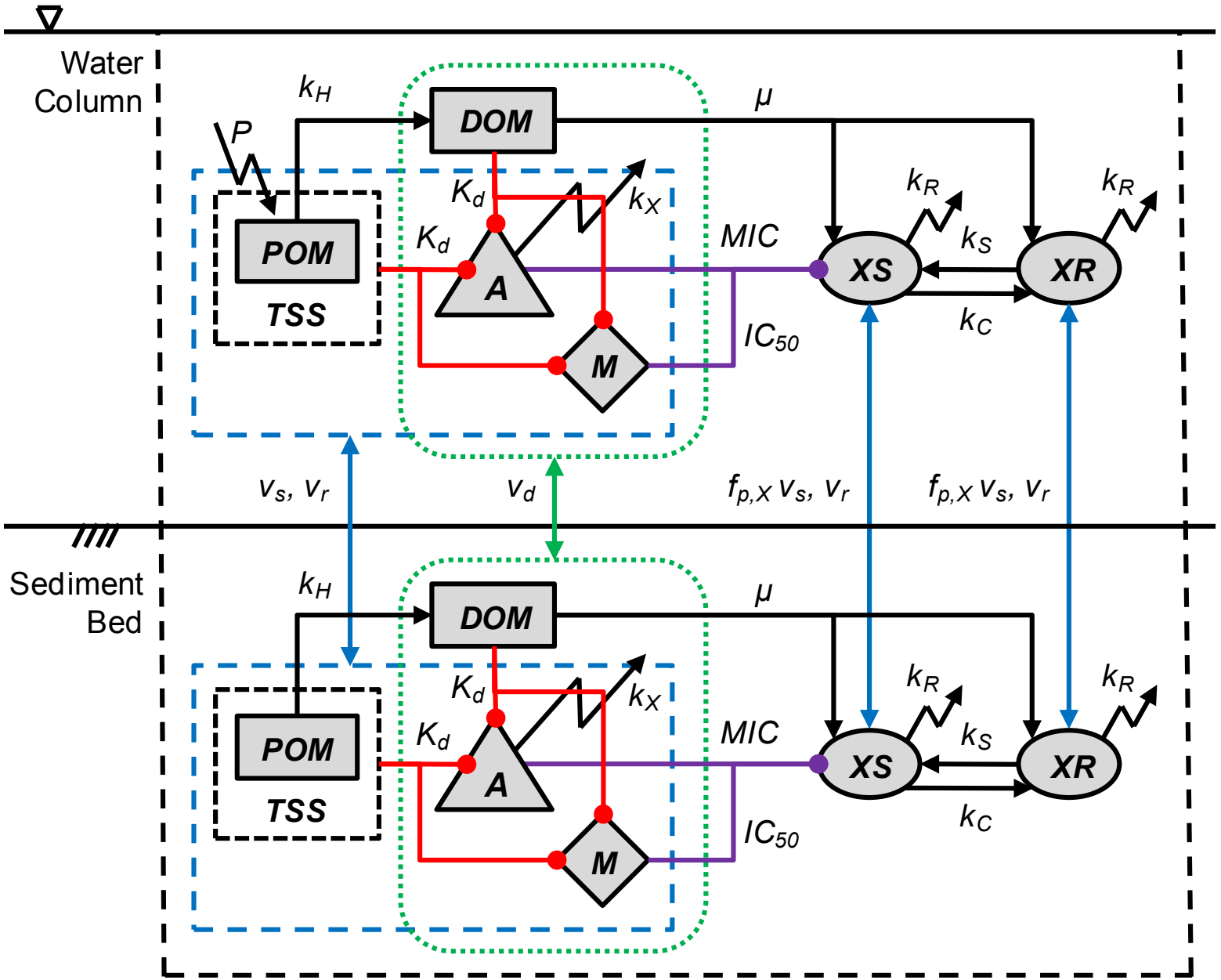
AR in the Context of Water Quality Modeling

Models are continuously evolving to address changing societal problems:



- Dissolved Oxygen (Streeter-Phelps)
- Pathogens
- Eutrophication
- Toxics (e.g. PCBs)
- Heavy metals
- Harmful algae (e.g. cyanobacteria)
- Pharmaceuticals and Personal Care Products (PPCPs)
- Antibiotic resistance

MAQUIS model



Some equations

$$\frac{dXS}{dt} = \mu_S XS - k_R XS \qquad \frac{dXR}{dt} = \mu_R XR - k_R XR$$

Antibiotic Effect[(a)] Metals Effect[(b)]

$$\mu_S = \mu_{MAX}\left(\frac{DOM}{K_M + DOM}\right)\left(1 - \frac{A_{fd}}{MIC_{fd}} - \frac{M_{fd}}{2 \times IC_{50}}\right)$$

$$\mu_R = \mu_{MAX}\left(\frac{DOM}{K_M + DOM}\right)(1-\alpha)$$

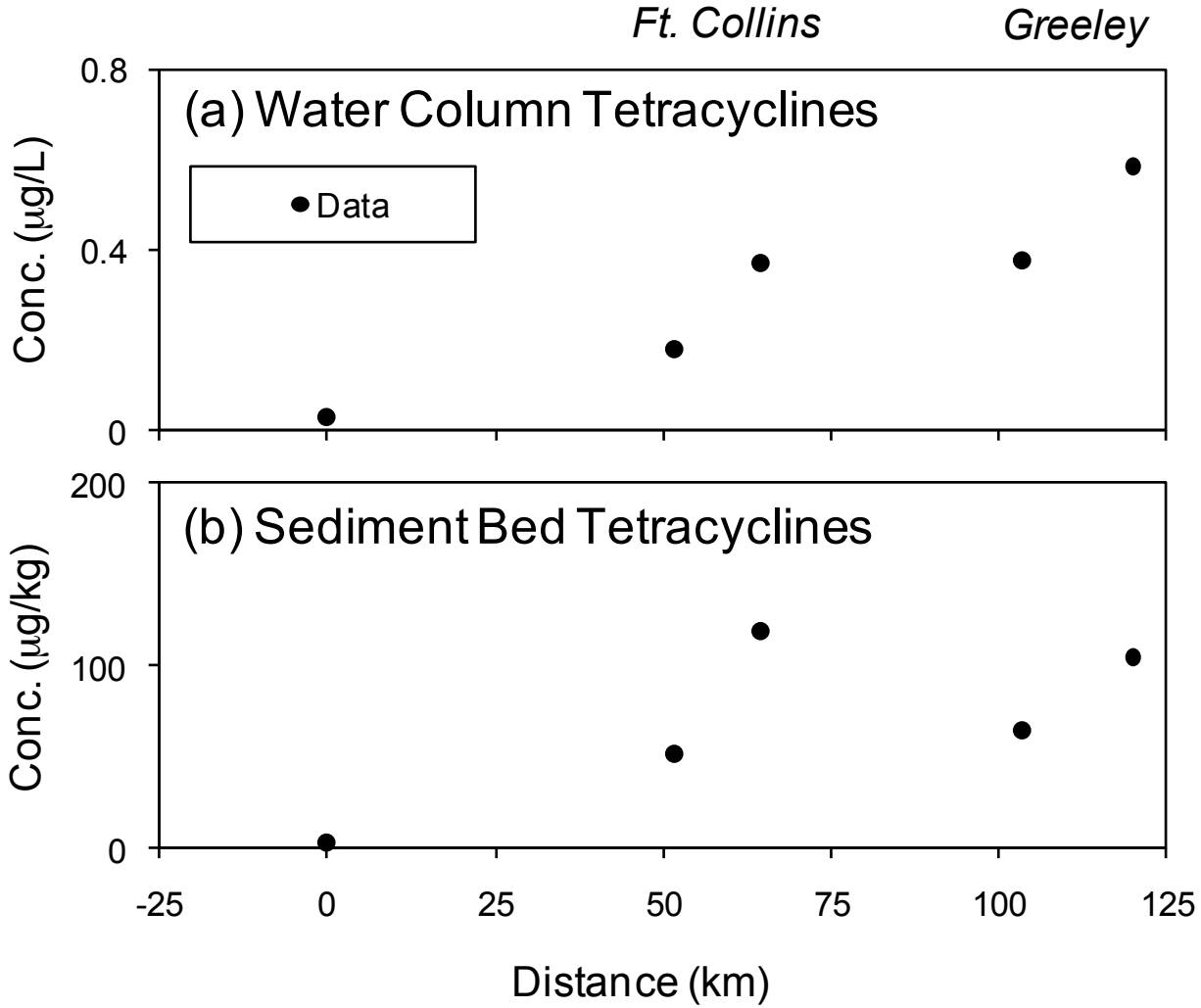
cost of carrying Resistance[(c)]

[(a)]Garrett et al. (1966). [(b)]Codina et al. (1993). [(c)]Stewart and Levin (1977).

Poudre River application - overview

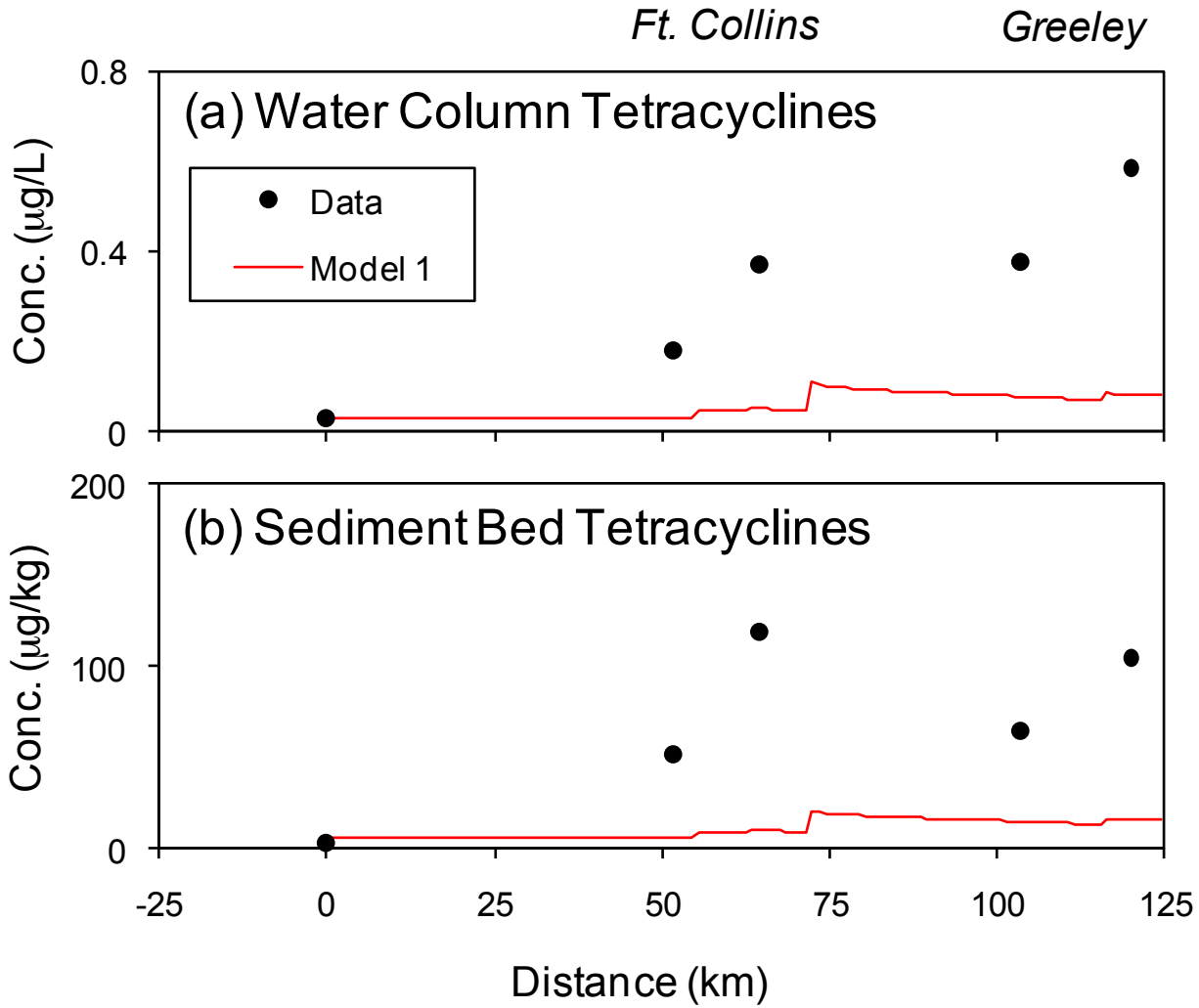
- All data from Yang and Carlson (2003), Kim and Carlson (2007, 2007b), Pruden et al. (2006) and Pei et al. (2006).

Poudre River application - tetracyclines



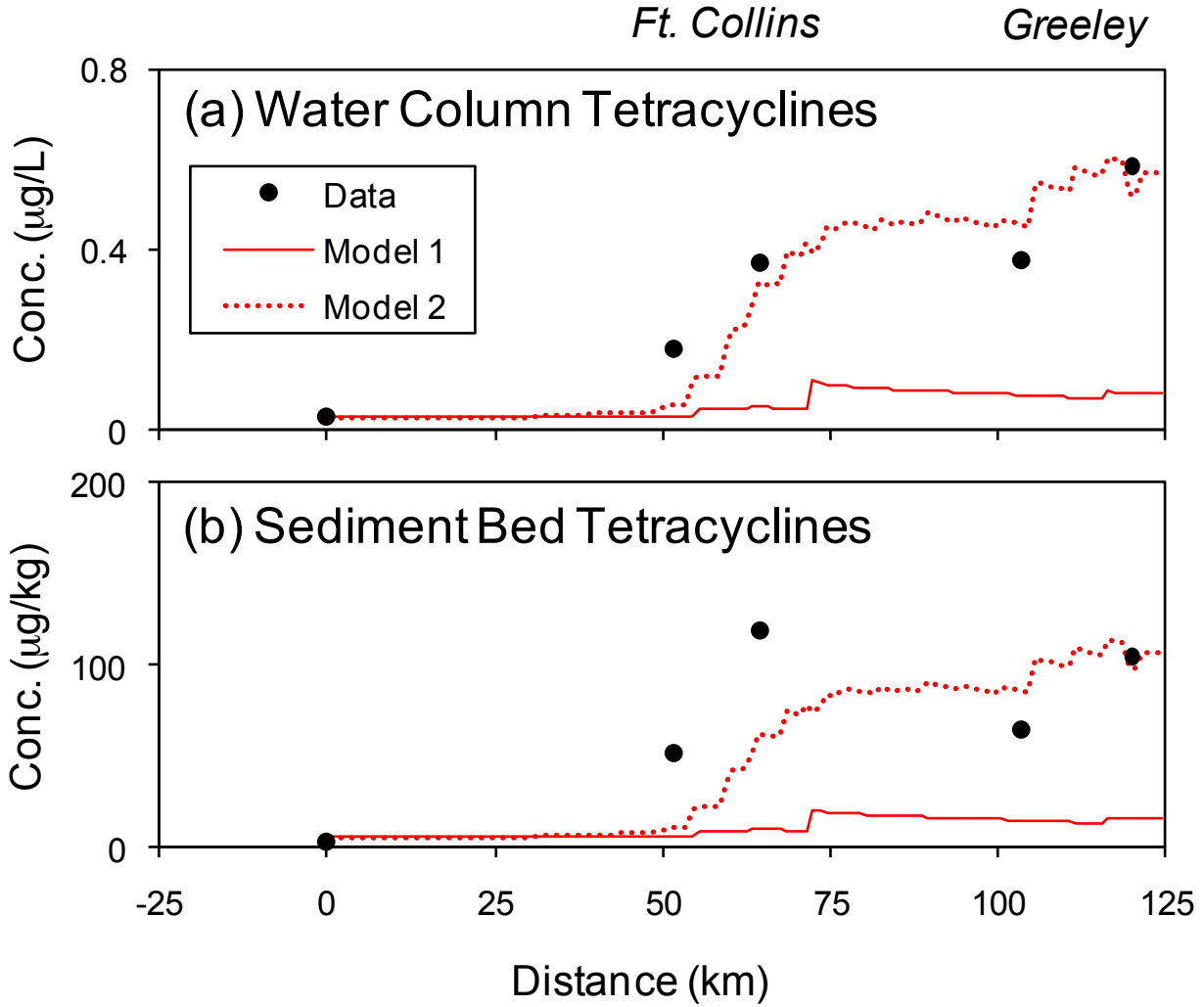
- Modeling sum of 6 tetracyclines

Poudre River application - tetracyclines



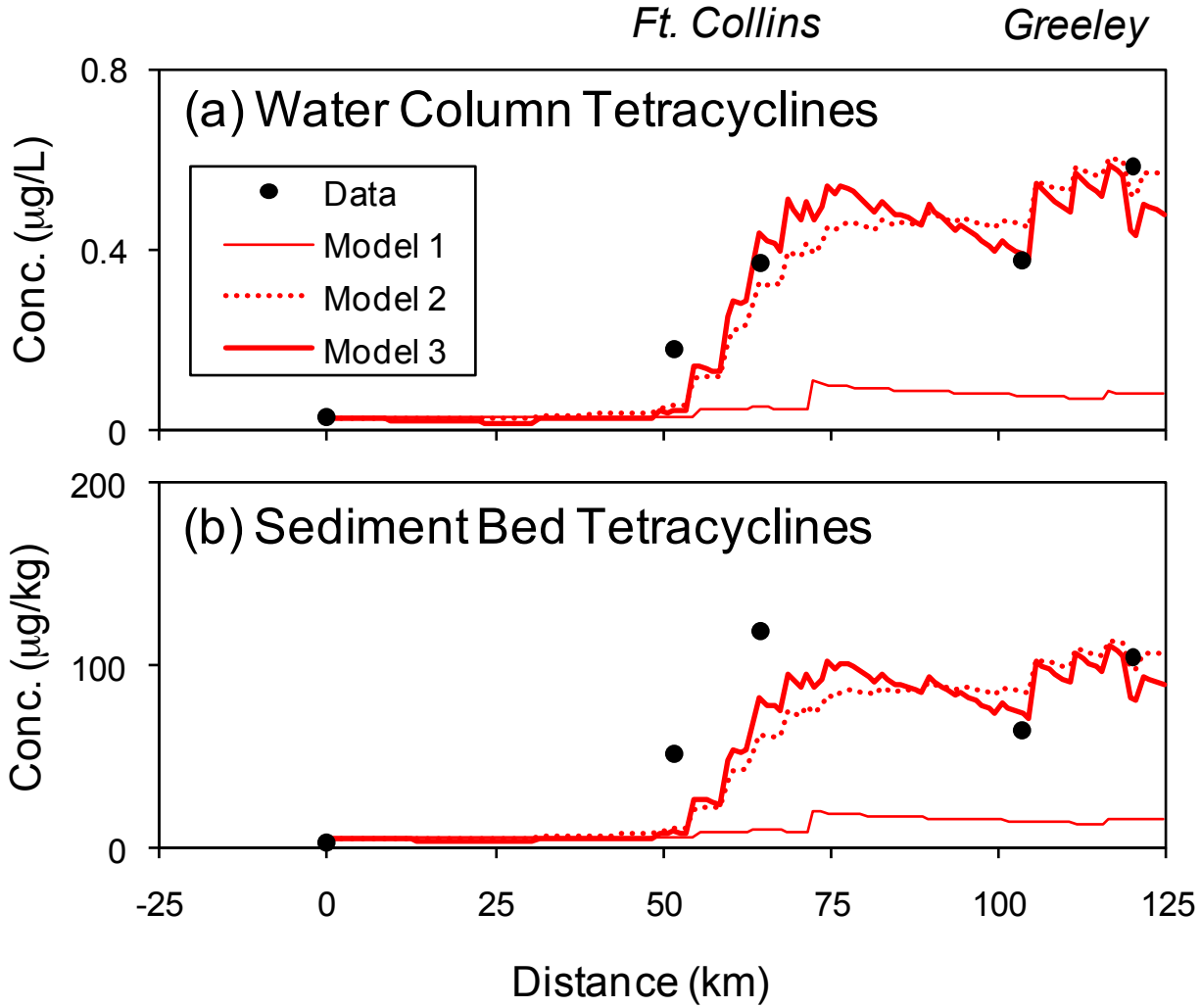
- Model 1 = Max. WWTP, no AG/CAFO, no decay

Poudre River application - tetracyclines



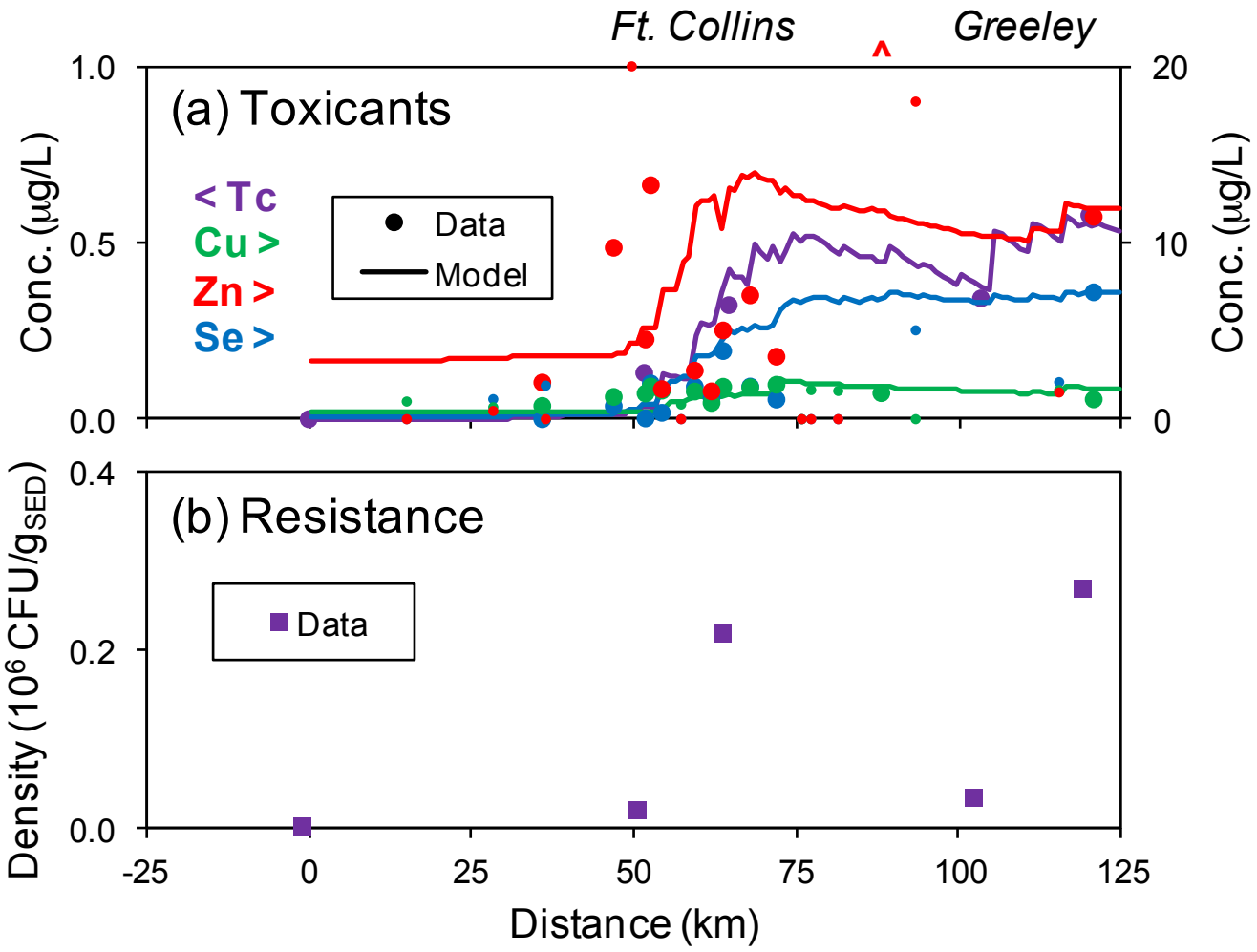
- Model 2 = Ave. WWTP, calib. AG/CAFO, no decay

Poudre River application - tetracyclines



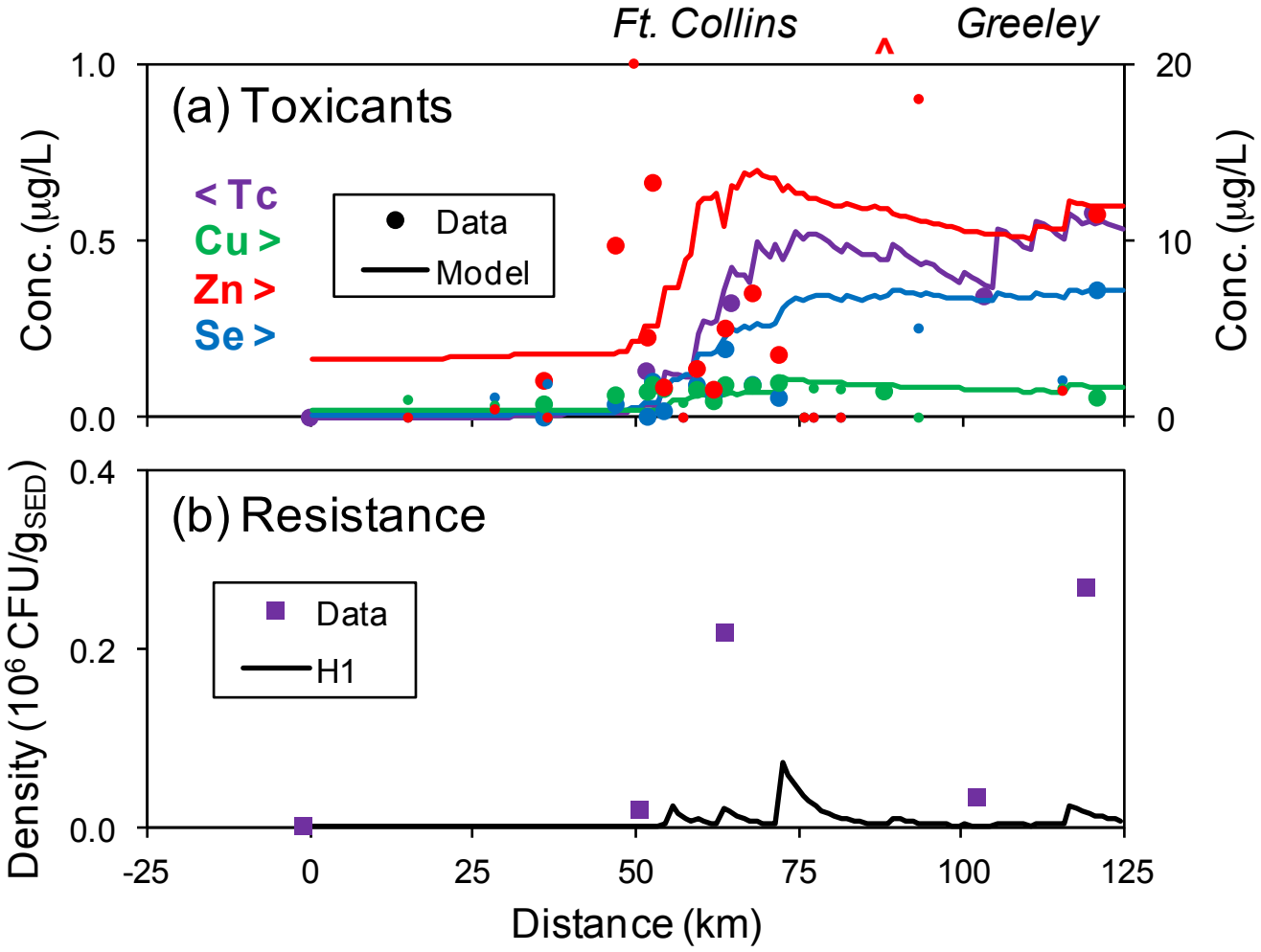
- Model 3 = Ave. WWTP, calib. AG/CAFO, decay

Poudre River application - resistance



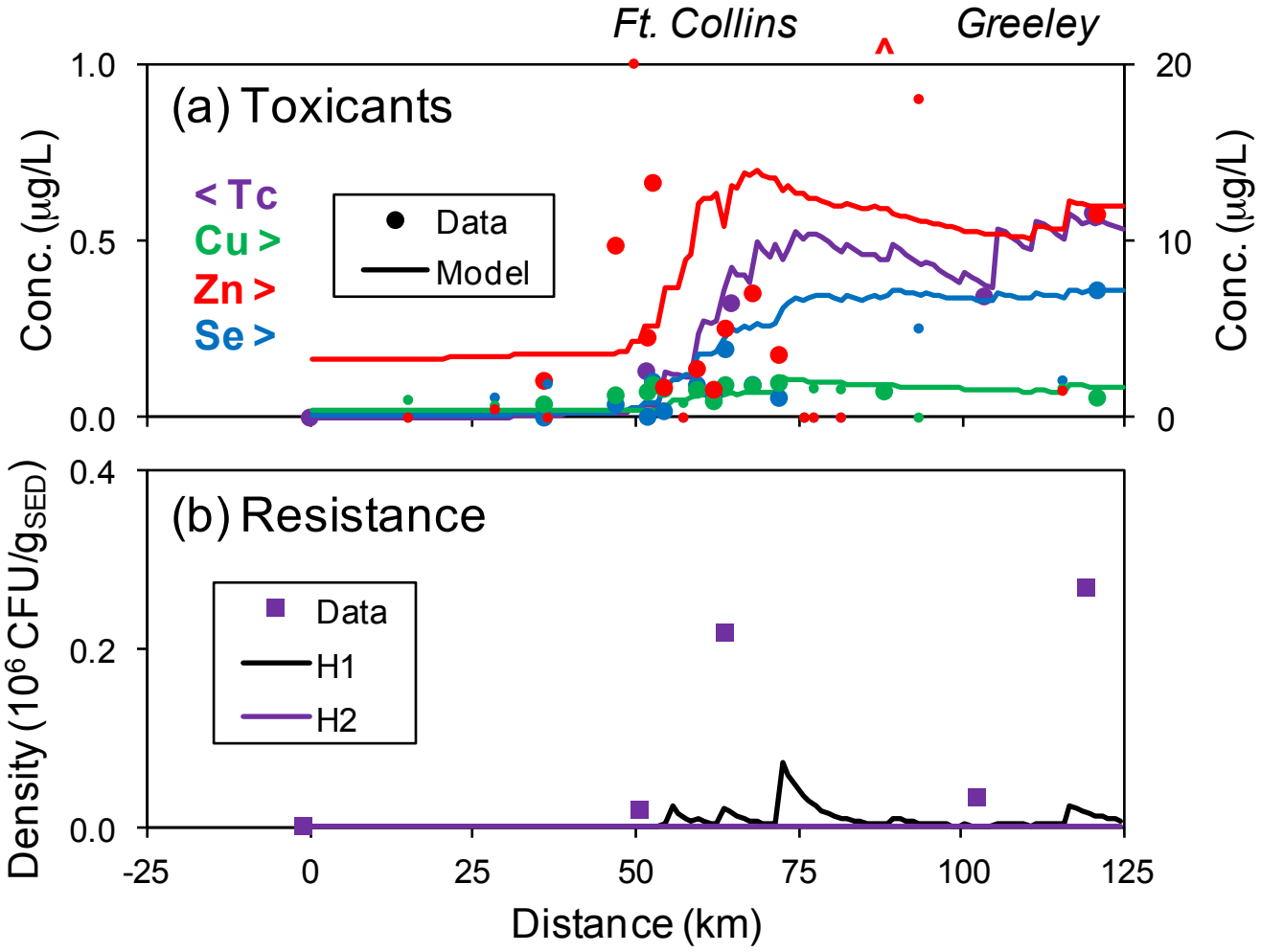
- Toxicant concentrations

Poudre River application - resistance



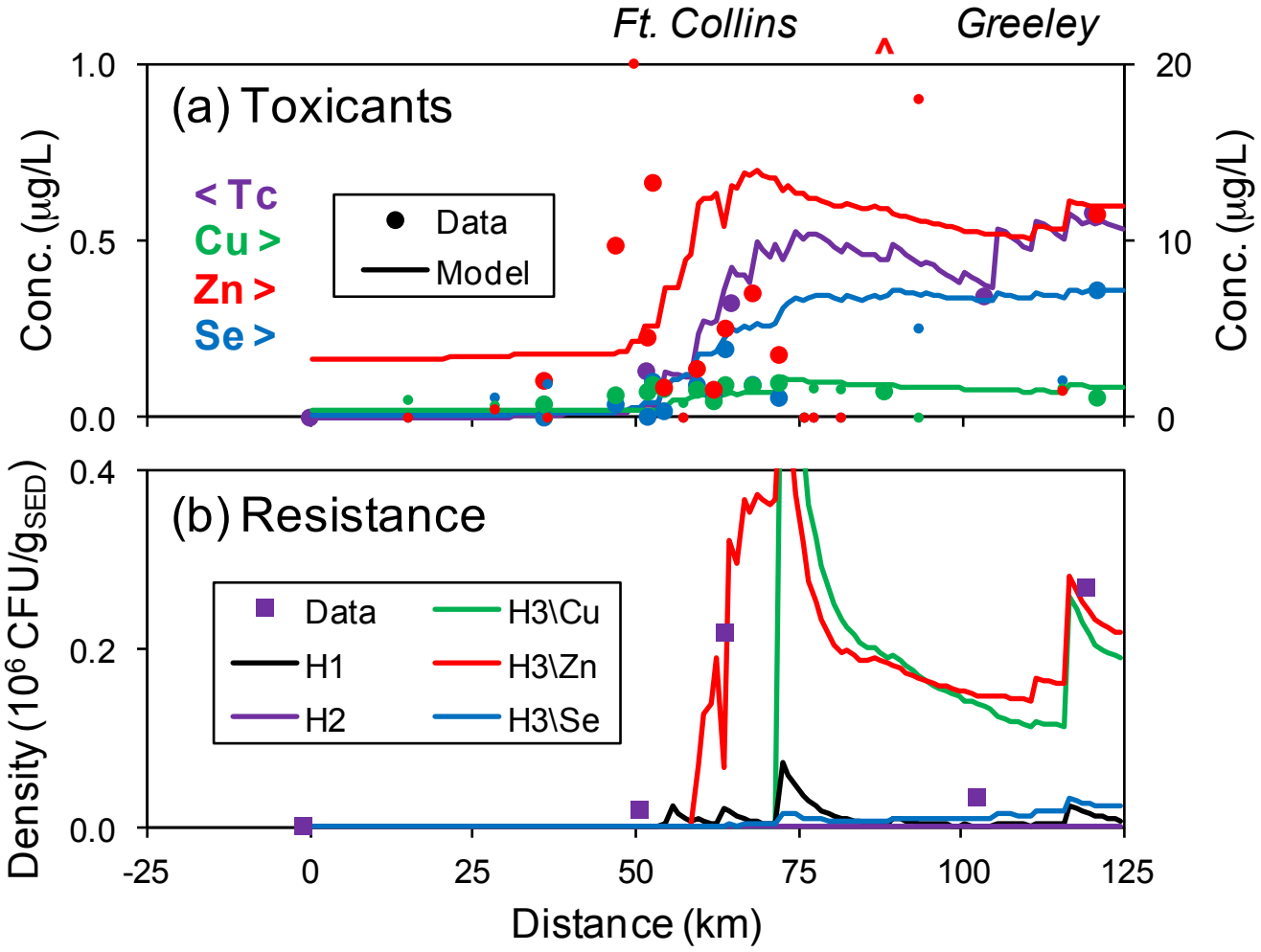
- Model H1 = Max. fraction resistant in input, no growth

Poudre River application - resistance



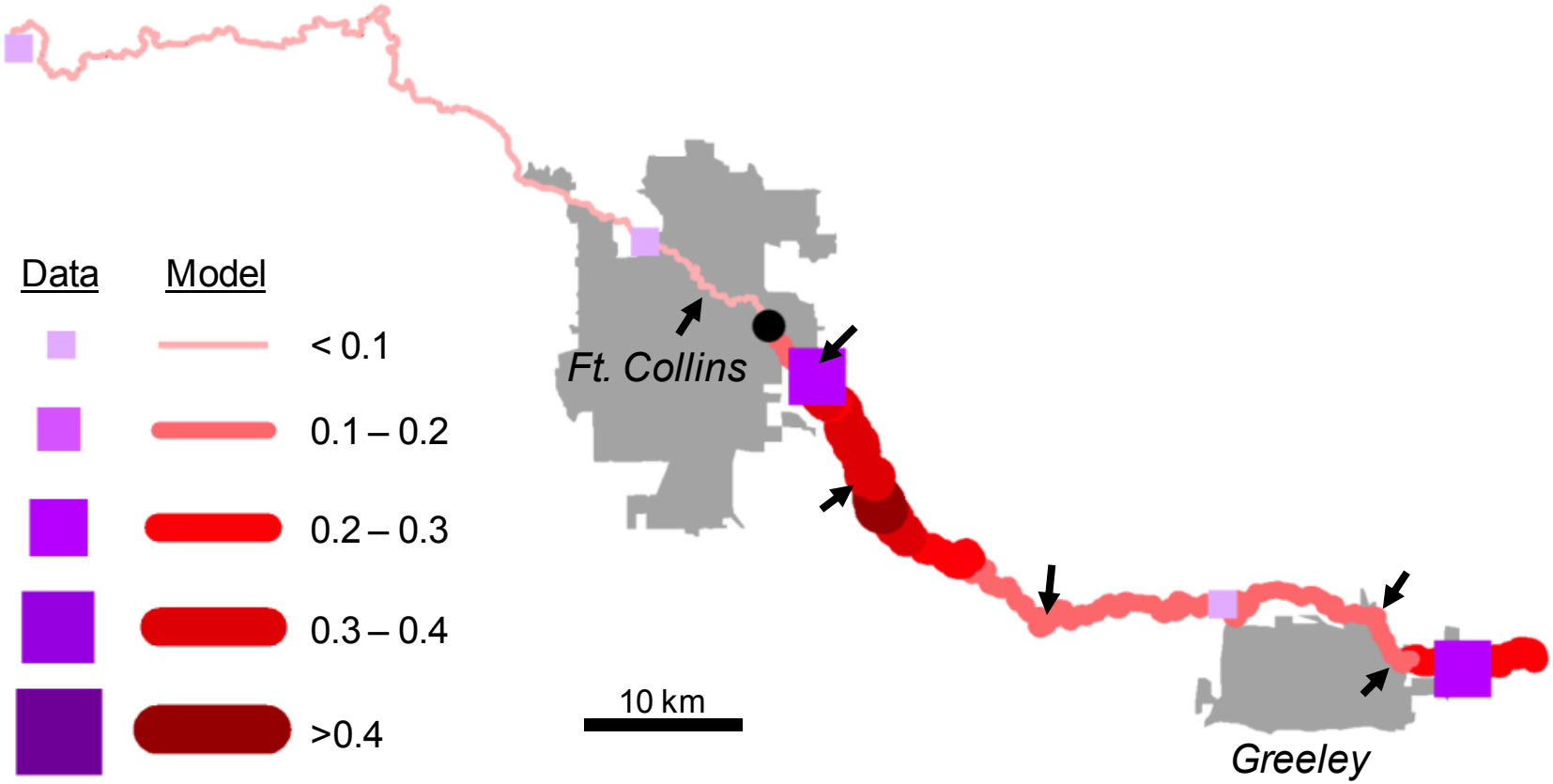
- Model H2 = Selection by antibiotics

Poudre River application - resistance



- Model H3 = Selection by metals

Poudre River application - resistance



- Model H3\Zn = Selection by Zn

Data from Pei et al. (2006).

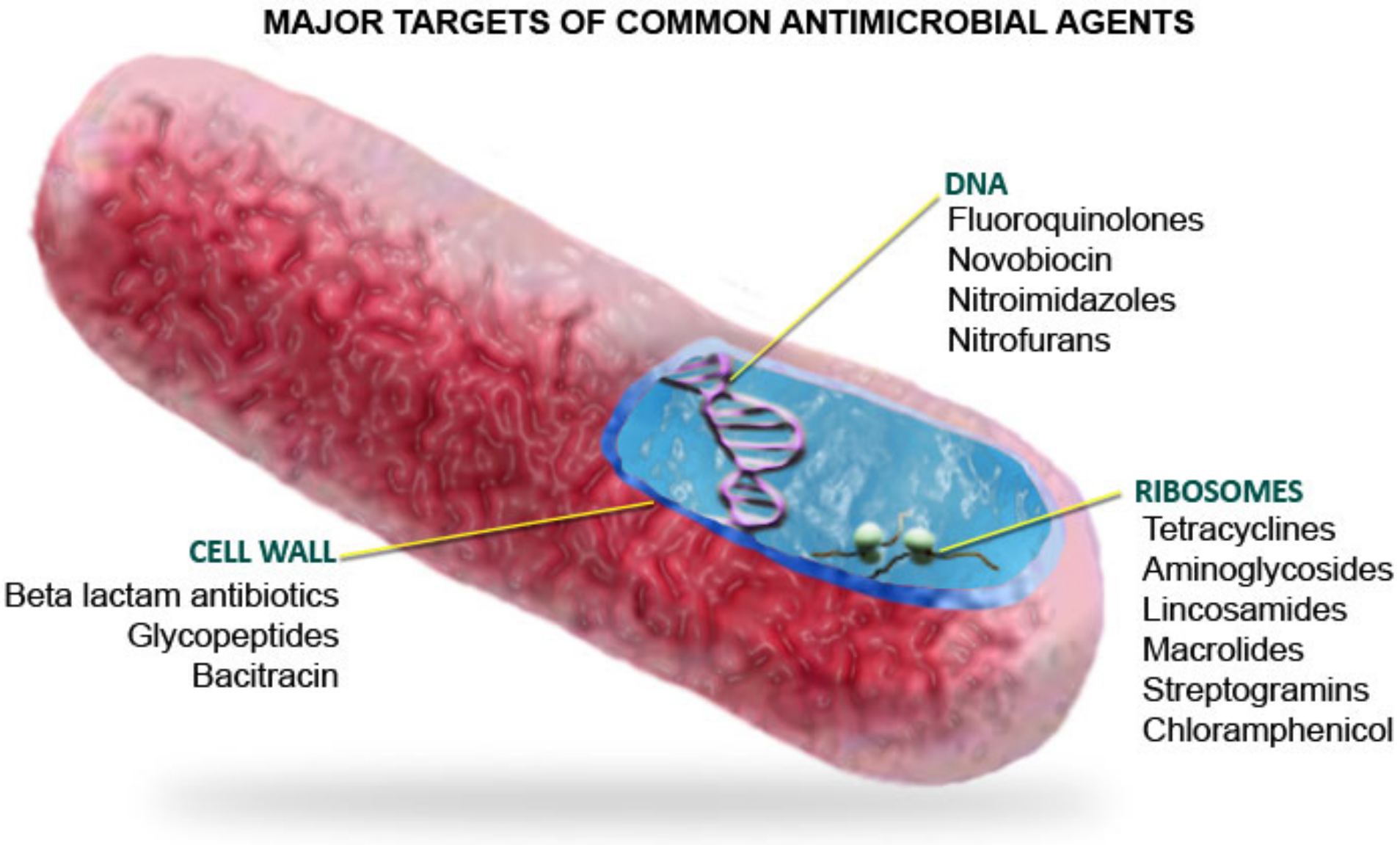
Conclusions (part 1/2)

1. Density of antibiotic resistant bacteria can NOT be explained by input alone (H1) or selection by antibiotics (H2).

2. Density of antibiotic resistant bacteria can be explained by selection by metals (H2), specifically Cu and Zn but not Se.

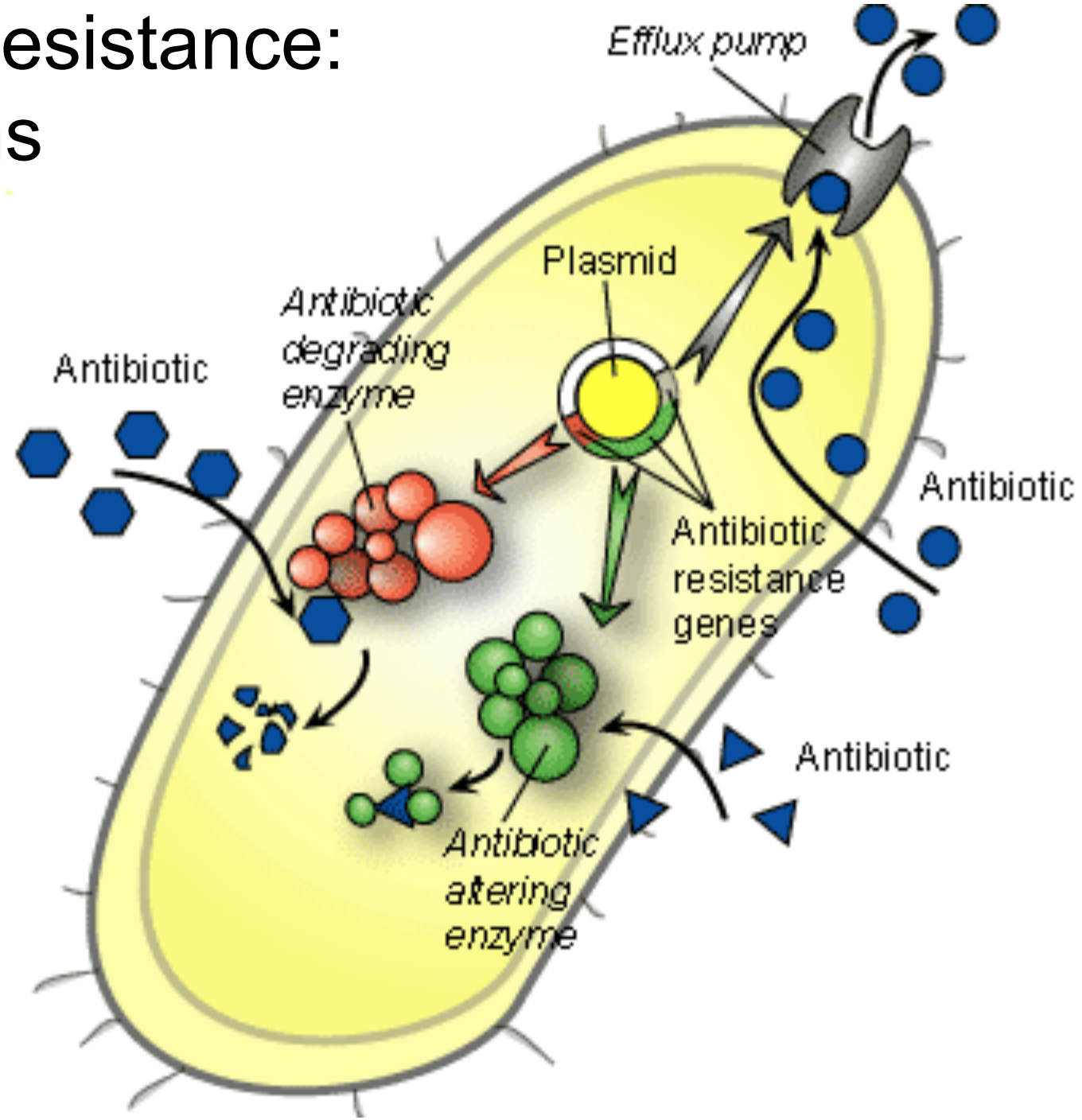
3. Significant parameter uncertainty, mostly in cost of resistance…

Antibiotics: Mechanisms



http://amrls.cvm.msu.edu/pharmacology/antimicrobials/mode-of-action

Antibiotic Resistance: Mechanisms



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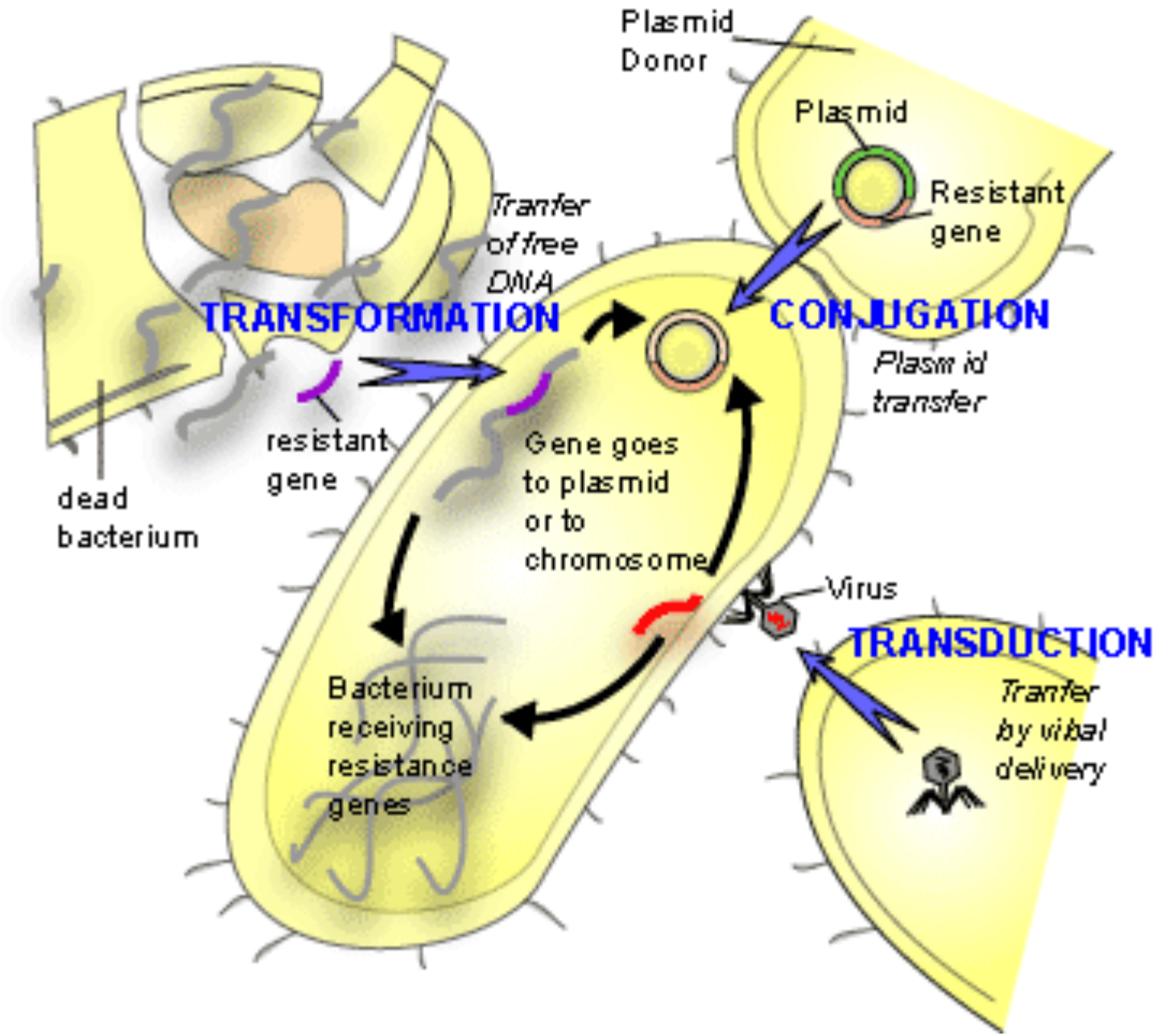
Antibiotic Resistance: Transfer



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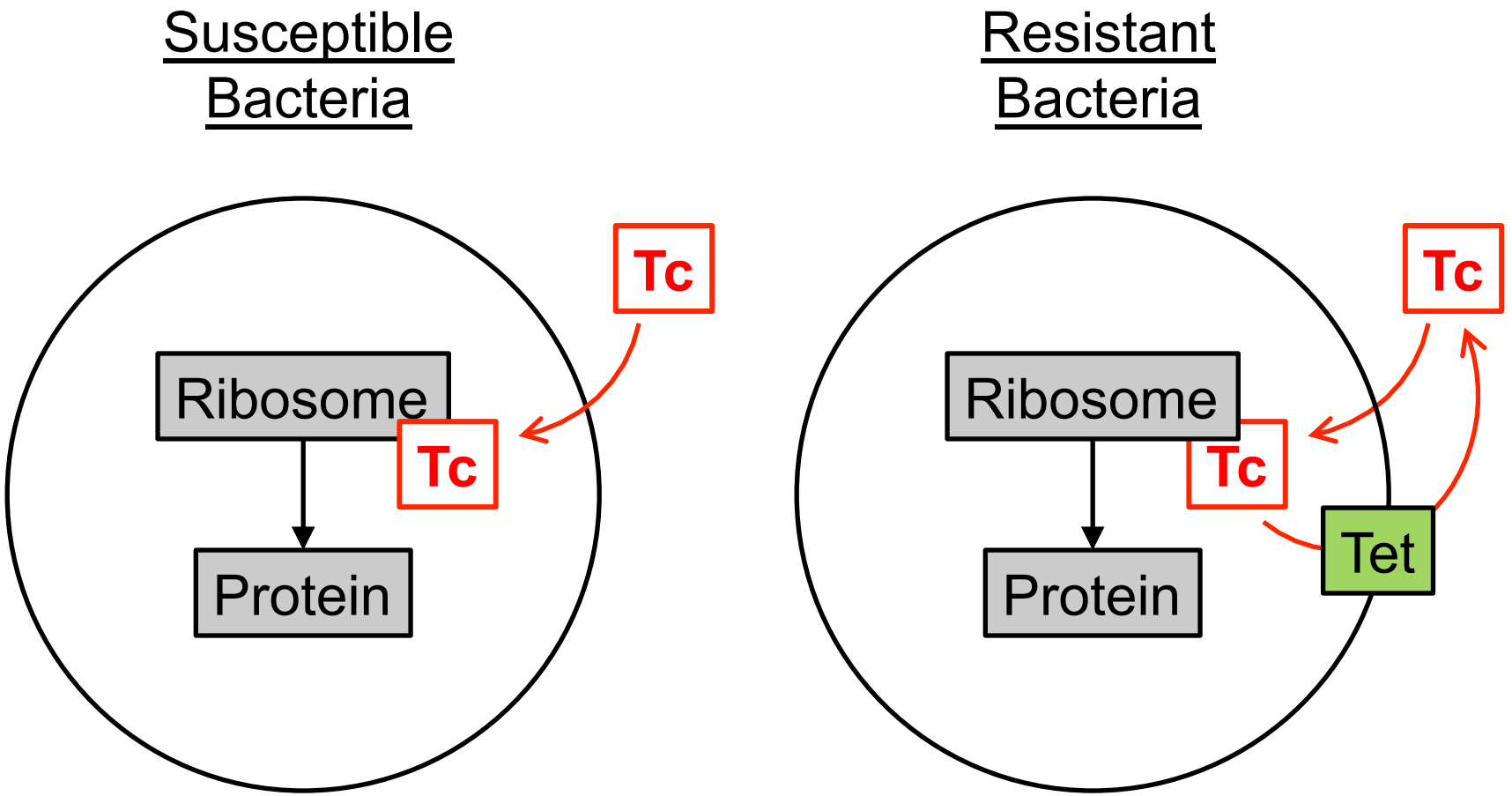
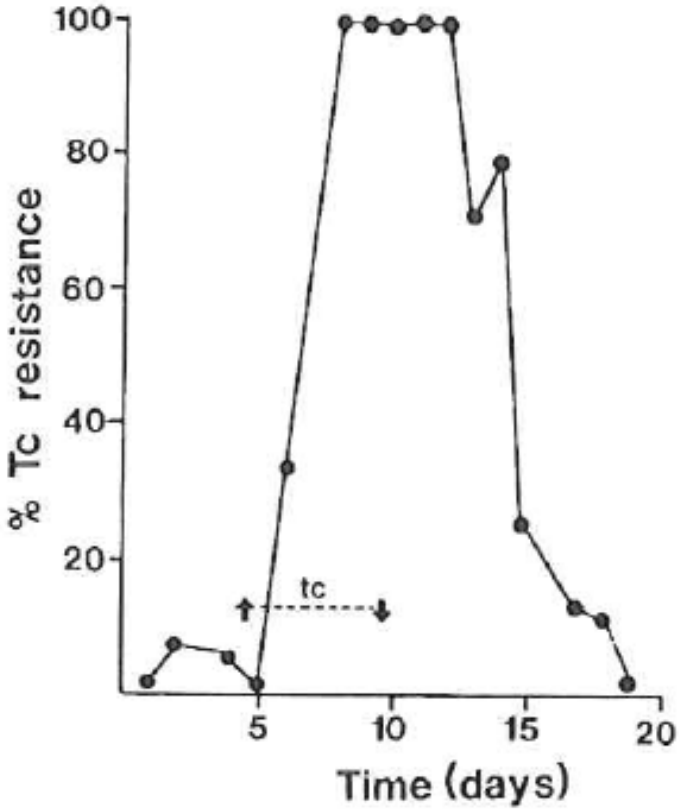
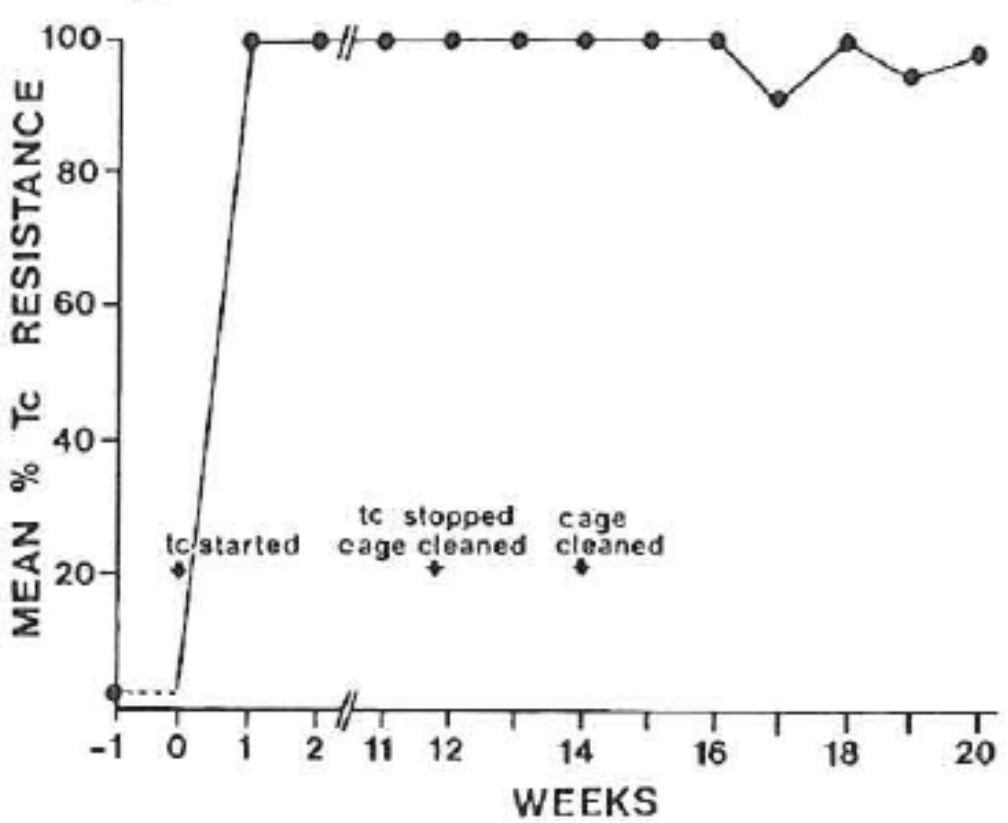
Plasmid-encoded tetracycline resistance in *E. coli*



When antibiotic is turned on/off…





Levy (1986)

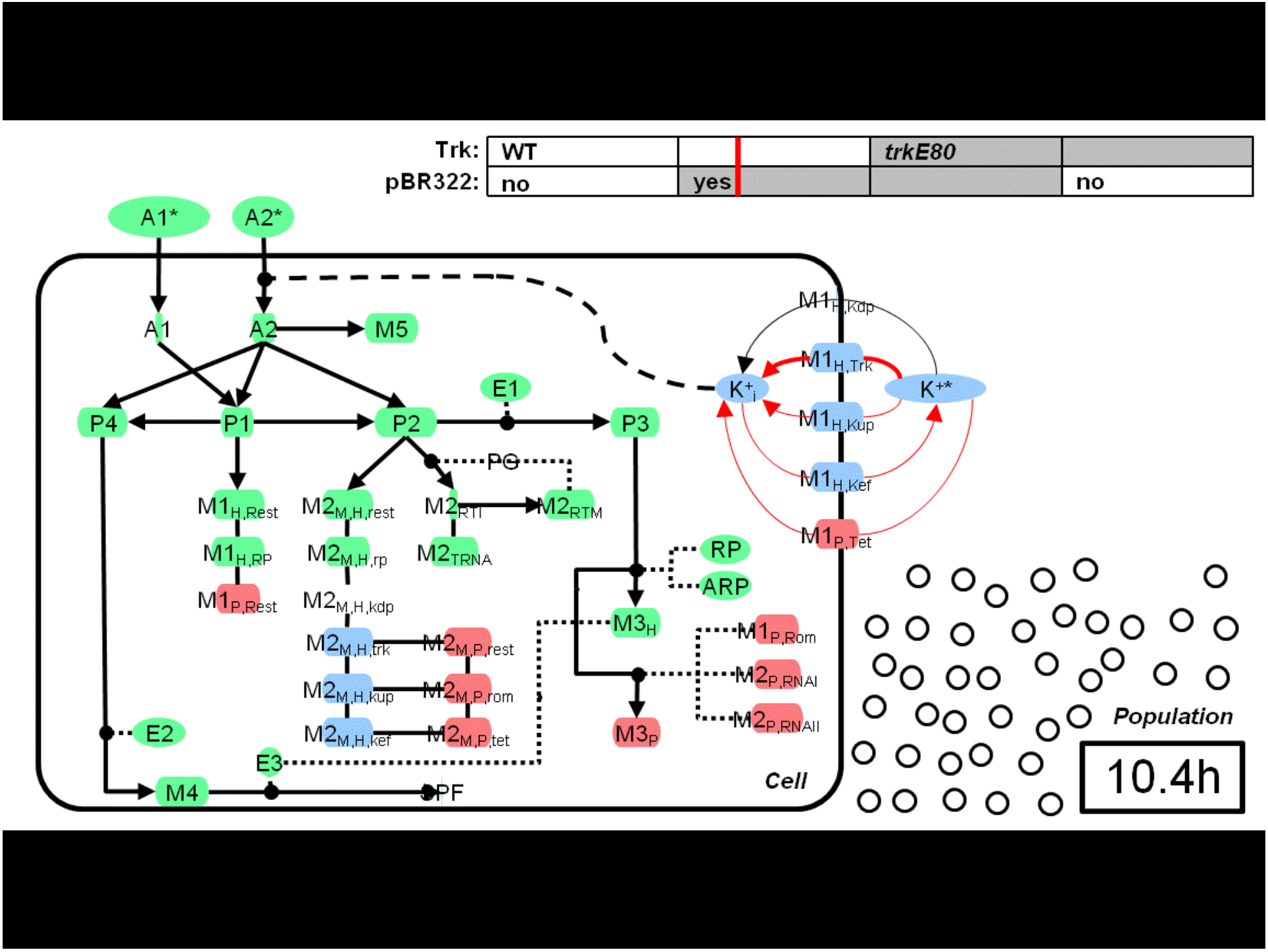
Evidence

- *E. coli* pBR322 (*tetA* class C efflux pump)
- Lenski et al. (2004)*
  - Competition without tetracycline
  - Naïve: susceptible > resistant
  - 500 generations of evolution
  - Evolved: resistant > susceptible
  - Mutation is on chromosome
  - Requires intact *tetA* on plasmid
- Dosch et al. (1984)*
  - Tet can mediate K^+ uptake

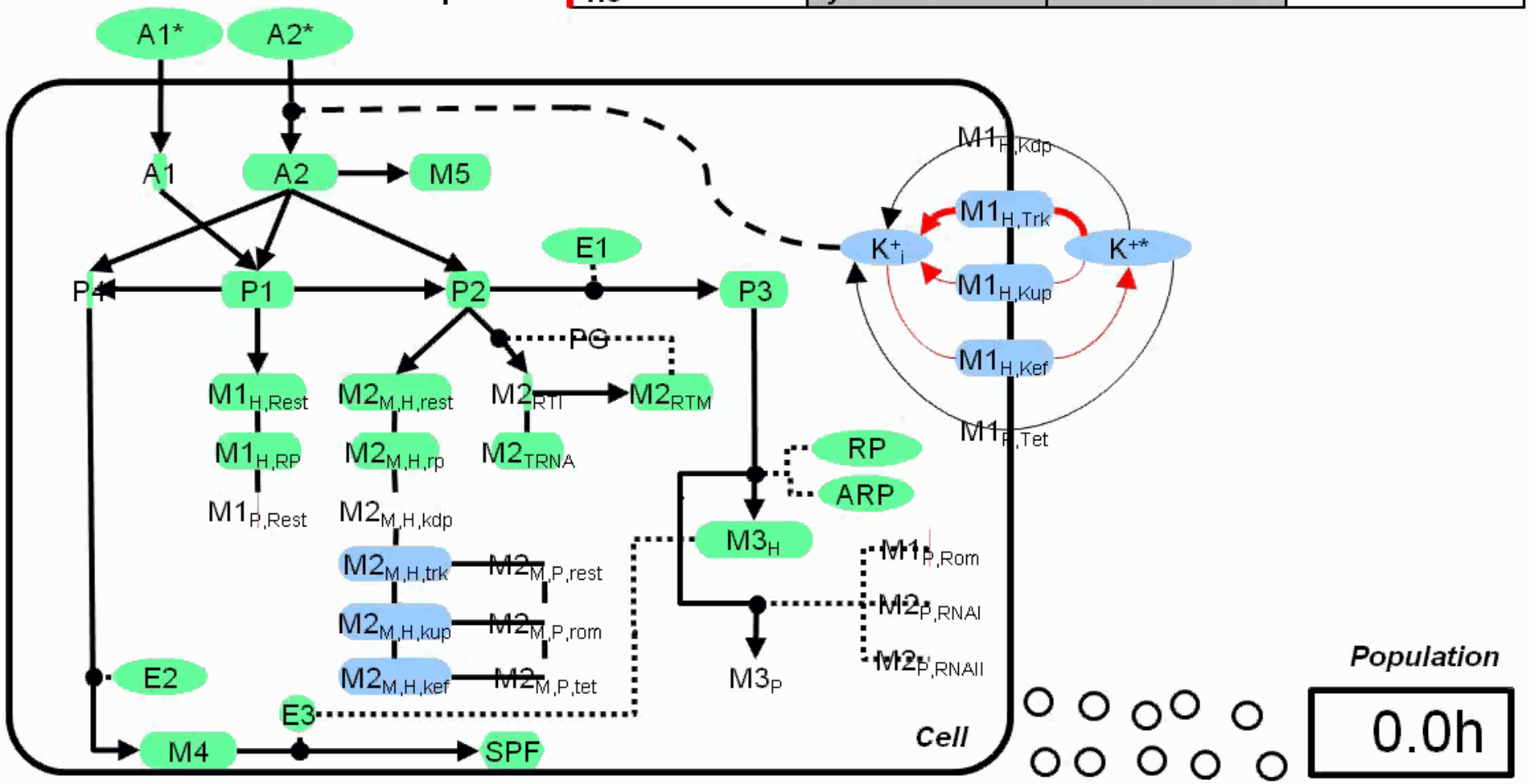
*Repeatable

Hypothesis

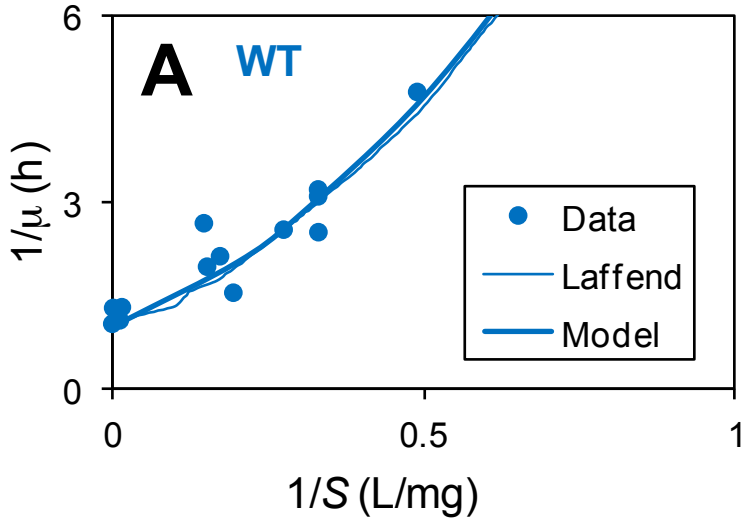
- Observed adaption is due to mutation in endogenous K^+ uptake system Trk
  1. Tet is somehow better than Trk
  2. Trk is redundant and costly plasmid-bearing cell
  3. Trk mutates
  4. Cell is dependent on Tet and plasmid

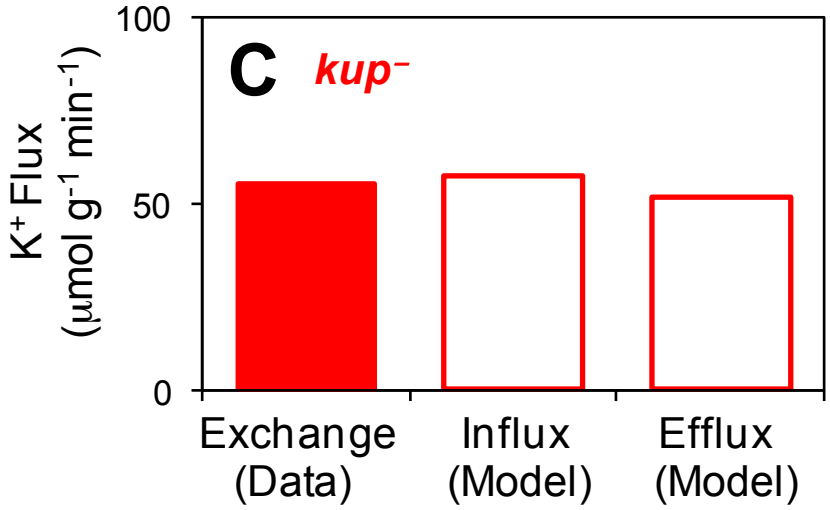

Trk:
WT
trkE80
pBR322:
no
yes
no
A1*
A2*
A1
A2
M5
P4
P1
P2
E1
P3
PG
M1H,Rest
M2M,H,rest
M2RTI
M2RTM
M1H,RP
M2M,H,rp
M2TRNA
M1P,Rest
M2M,H,kdp
M2M,H,trk
M2M,P,rest
M2M,H,kup
M2M,P,rom
M2M,H,kef
M2M,P,tet
E2
E3
M4
PF
M3H
M3P
RP
ARP
M1P,Rom
M2P,RNAI
M2P,RNAII
Cell
M1H,Kdp
M1H,Trk
M1H,Kup
M1H,Kef
M1P,Tet
K+i
K+*
Population
10.4h

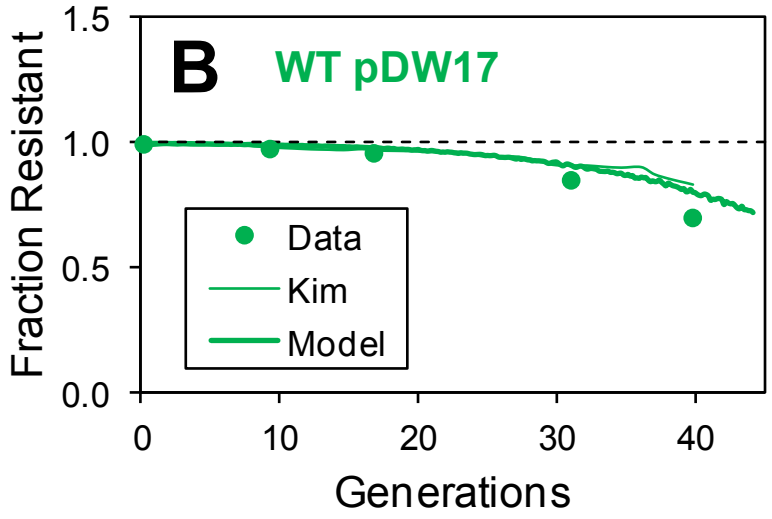
Trk:	WT		*trkE80*	
pBR322:	no	yes		no

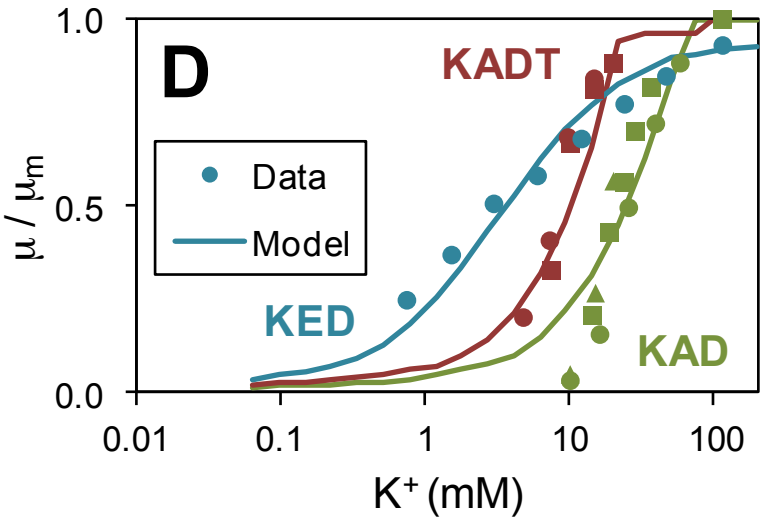


Results: General behavior



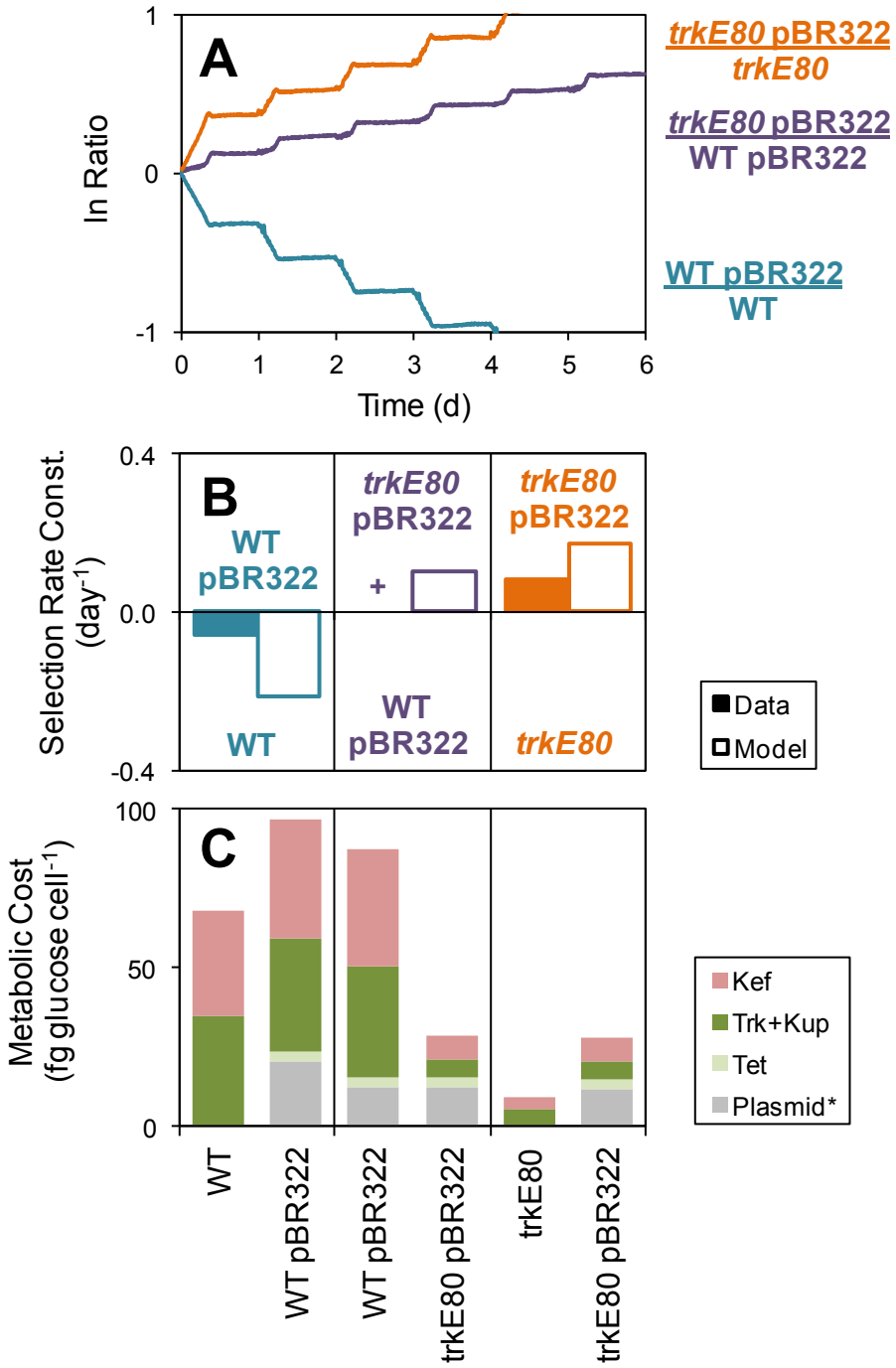






Data and other models from Domach et al. (1984), Laffend & Shuler (1994), Kim & Shuler (1990), Rhoads & Epstein (1978), Dosch et al. (1984, 1991).

Results: Competitions



Data from Lenski et al. (1994).

Conclusions (part 2/2)

4. Metabolic modeling can explain cost of resistance and adaption (for simple laboratory cases).